PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Performance of syndromic management for the detection and treatment of genital Chlamydia trachomatis, Neisseria gonorrhoeae and Trichomonas vaginalis among women attending antenatal, well woman and sexual health clinics in Papua New Guinea: a cross-sectional study.
AUTHORS	Vallely, Lisa; Toliman, Pamela; Ryan, Claire; Rai, Glennis; Wapling, Johanna; Gabuzzi, Josephine; Allen, Joyce; opa, Christine; Munnull, Gloria; Kaima, Petronia; Kombuk, Benny; Kumbia, Antonia; Kombati, Zure; Law, Greg; Kelly-Hanku, Angela; Wand, Handan; Siba, Peter; Mola, Glen; Kaldor, John; Vallely, Andrew

VERSION 1 – REVIEW

REVIEWER	Remco Peters Anova Health Institute, Johannesburg, South Africa
REVIEW RETURNED	07-Aug-2017

GENERAL COMMENTS	This interesting manuscript by Vallely and colleagues assesses the performance of syndromic guidelines for management of STIs in Papua new Guinea. The authors demonstrate the limited performance of this approach in their context based on three populations: ANC visitors, well women and sexual health clinic attendees. Although the limited value of syndromic management has been reasonably well-documented, there are limited data for the Asian-Pacific region. Moreover, the comparison of performance in three different groups adds strength to the manuscript. I have some comments that may help improve the manuscript. Major comments The availability of data from three different populations is strength of the paper. However, Table 1 illustrates that these populations are very different with regards to bio-behavioural data (e.g. age, sex for money, etc.). Therefore, I think it is not appropriate to aggregate data anywhere in the manuscript (e.g. overall STI prevalence, overall prevalence of symptoms). Data should be presented stratified by study settings as is also done in table 4. The methods section would benefit of additional information with regards to the three study settings: which 'type' of women usually access these services? Are these only for screening purpose or do only for symptomatic women? Also, 'well woman' clinic is not a widely known concept – what does this entail?

	The results section would benefit from more detailed and structured information with regards to a) prevalence of symptoms (and which ones), and b) proportion of symptomatic/asymptomatic infections in each study population. The conclusion (see strengths box at the first page) is that asymptomatic infections constitute a problem as these are not treated under the syndromic approach, but nowhere is clearly mentioned which proportion is (a)symptomtic. We know that performance of this algorithm for STIs is not going to be perfect due to a) asymptomatic infections, b) other (non)STIs causing similar symptoms. The use of these syndromic guidelines is not to 'detect' or 'diagnose' STIs, but to provide a basis for empirical treatment that may be correct or incorrect. Therefore, I think an outcome with regards to 'proportion correctly treated' and 'proportion overtreatment' (antibiotics given based on algorithm but none of the STIs present) and 'proportion undertreatment' (STI+ but not treated or treated with incorrect antibiotics based on the algorithm) may be more appropriate that the sens/spec/ppv/npv. In addition to previous comment: it would be more appropriate to calculate the sens/spec/ppv/npv of the algorithm in symptomatic women only. Asymptomatic women would inherently be missed, setting the algorithm up for failure, but the question is still: how does the algorithm perform in symptomatic women? (Figure of speech: if this were to be good, the syndromic guidelines would still be useful). The results section could be condensed, especially description of the results in table 4; the highlights of this table could be presented in a few sentences instead of full page. This would allow to add some information (see previous paragraph). Would it be valuable for the authors to design a risk score based on the bio-behavioural and clinical data, using multiple regression analysis, to see if they could generate a (syndromic) algorithm with better performance in their context? The authors should decide about what they do with their HIV and syphilis data. Venepuncture is mentioned in the abstract, and HIV and lues testing in the results section, but they do not seem to present these data. Perhaps include these in table 1 with demographics? Would delete 'venepuncture' from the abstract. In addition to previous comment: dependent on the HIV prevalence: did they see a difference in performance of the algorithm between HIV+ and HIV- women? And did ART play a role? Minor comments. Abstract, objective: abbreviation PNG is not introduced earlier. Abstract: include reference to WHO guidelines as the reference standard. References 1 and 2 appear missing from the introduction section, as the first reference mentioned is number 3. How were the STIs diagnosed? Don't understand the mention of venepuncture in the methods section, which would suggest serology played a role? Introduction speaks of 'underdiagnosis' which should read 'undertreatment' as the syndromic algorithms do not provide a diagnosis but treat empirically. Same for the last sentence of the introduction that provides the 'objective' of the paper: it's not about detecting STIs, but it's an indication for presumptive treatment that covers STIs. Please elaborate on reference 12 and include a bit more information about the laboratory tests used to detect CT, NG and TV, include the name of the assay(s).

	Do the authors have any information about time since onset of symptoms? Does this impact on the performance of the algorithm? What drugs are used in Papua New Guinea to treat STIs? And how are women with a previous/recent history of STI treatment evaluated in this algorithm? Did this affect performance of the algorithm? The authors mention that BV and MG were not looked at in their study, but perhaps should also mention Candida infections. There is a recently published systematic review of the WHO syndromic guideline for vaginal discharge syndrome in PLoS that should be added to the reference list.

REVIEWER	Nigel Garrett Centre of the AIDS Programme of Research in South Africa (CAPRISA), South Africa
REVIEW RETURNED	15-Aug-2017

GENERAL COMMENTS	The manuscript by Lisa Vallely and colleagues is a well written paper, which further highlights the inadequacies of the syndromic STI management care model in high burden and resource-constrained settings. This large cross-sectional evaluation was conducted among women presenting to three distinct clinical services in one of the highest STI burden countries (Papua New Guinea) globally. It confirms the high burden of STIs, and the low accuracy of predicting disease with the syndromic approach, and makes the case for a radical change to a point-of-care diagnostic care model. Although other groups have previously described the problems with syndromic management, this paper adds to the literature at an important time, when a switch to diagnostic testing is considered by the WHO. Major comments 1. page 4, line 38: Considering that most STI experts and the WHO agree that syndromic STI management is not ideal, it would be important to highlight some of the recent constructive discussions on how to transition from syndromic to diagnostic care. It may be worthwhile highlighting a recent WHO report ('Global health sector strategy on sexually transmitted infections 2016–2021. Towards ending STIs to the reader'). http://apps.who.int/iris/bitstream/10665/246296/1/WHO-RHR-16.09-eng.pdf?ua=1 2. The authors should clarify what happened to women who were asymptomatic, i.e. received no syndromic treatment, but were diagnosed with one of the three STIs. Were these women contacted and offered treatment? If this group was not offered treatment, it is important for the reader to know that this was clearly addressed/ discussed during the consent process for the study. 3. p.10, l.36: A high proportion of women reported abdominal pain (36.7%). This is higher than in previously reported studies, where vaginal discharge has been the most common symptom/sign. It would add to the manuscript, if the authors could expand on this phenomenon (in the results or discussion), in particular, whether they believe that the abdominal pain was due to PID (i.e. STI complication) or other causes, and whether these women received an extended course of antibiotics or not.

	Minor comments 1. Page 7, line 13: Consider switching NPV and PPV to be consistent with the tables. 2. Table 1: Please double-check variables ‘vaginal sex in the last week’ and ‘no. of people had vaginal sex with in the last week’. It looks like the number of women who had sex in the last week differs (N=1062 vs N=1109). If this is correct, it may be worth explaining the difference in a footnote, e.g. the data was based on questionnaire or similar. 3. p.15, l.41: The authors say that BV (a vaginal syndrome) is ‘sexually transmitted’. While there is strong evidence that BV is ‘associated’ with sex, it is not usually described as ‘sexually transmitted’. Detailed microbiome studies are currently investigating, whether there are specific anaerobes, which contribute to BV, that are indeed ‘sexually transmitted’. 4. p15, l.49: Suggest to abbreviate BV higher up in the manuscript. 5. Given the high rates of asymptomatic STIs among antenatal attendees, it would be useful to add to the discussion the implications thereof, some of which are only mentioned in the Introduction (e.g. premature labour and low birth weight).

REVIEWER	Jillian Pintye Department of Global Health, University of Washington, Seattle, USA
REVIEW RETURNED	22-Aug-2017

GENERAL COMMENTS	This is a well written paper about an important issue affecting women and infants worldwide. The authors present an evaluation of syndromic management of curable STIs among women attending ANC and SRH clinics in Papua New Guinea, a setting with significant STI burden. The methods are sound and the interpretation of results is appropriate. I have a few specific comments to strengthen this manuscript: Introduction 1. The authors state that PNG "...has among the highest estimated prevalences of genital chlamydia, gonorrhoea and trichomonas of any country in the Asia-Pacific region",. However, the actual % compared to that of other countries would be a stronger set up. Consider re-phrasing to, "The prevalence rates of CT, GC and TV within the Asia-Pacific region are XX%, XX% and XX%, respectively. Among all countries within the region, PNG is among the highest prevalence countries for all three infections with rates of XX% for CT, XX% for GC and XX% for TV" or something to that effect that compares the PNG rates with the overall regional rates. Study design and procedures 2. It's important that to distinguish that you are evaluating "diagnostic" performance of syndromic algorithms rather than other types of performance (ie economic, etc). I suggest include "diagnostic" when indicating that you are evaluating "performance".

	3. How and when were PCR results returned to clients? Were antimicrobials administered to participants free of charge? Were all clients treated? It is important to include these details or at least note that participants with lab-confirmed infections were treated per PNG Ministry of Health guidelines and then cite the guidelines. Results 4. Appropriately, the results are presented stratified by clinic entry point. It would be helpful to reference the rationale for this approach in the methods and perhaps even in the intro (ie prevalence rates vary by female subpopulations and may present differently and/or have different epidemiological trends). As is, it's not clear why the authors decided to present the results stratified as this approach is only introduced in the results. Discussion 5. The first paragraph is mainly restating the findings. It is very helpful to include the impact statements (ie XX% of infections would have been missed without lab testing), but it would also be helpful to tie these findings to a larger public health message. For example, why does it matter that so many infections would be missed? How might this contribute to the overall burden of adverse perinatal/MCH outcomes in this setting? Are these findings different than other similar studies or rather to they contribute to the growing evidence that additional POC diagnostics are needed for STIs, specifically within the context of ANC, etc? These details would strengthen the discussion's first paragraph rather than simply restating the results. 6. The organization of the discussion could be strengthened. It seems odd to call out the lack of M. gen and BV testing but not discuss the other very interesting findings. For example, the prevalence of CT is quite high (>20%) among ANC clients and then low (~7%) among well women. Was this finding expected? How does this compare to similar settings? A discussion about these results are warranted rather then the BV and M. gen details as the evidence base for those STIs causing adverse perinatal outcomes is less strong than CT, GC, and TV. 7. Condense the limitations to one paragraph and raise these concerns later in the discussion, after grounding your findings to the existing literature and explaining the implications of your results (ie need for further POC testing in LMICs, substantial burden of STIs associated with adverse perinatal outcomes among pregnant women, etc).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Remco Peters
Institution and Country: Anova Health Institute, Johannesburg, South Africa
Please state any competing interests: I do not have any competing interests to declare.

This interesting manuscript by Vallely and colleagues assesses the performance of syndromic guidelines for management of STIs in Papua new Guinea. The authors demonstrate the limited performance of this approach in their context based on three populations: ANC visitors, well women and sexual health clinic attendees. Although the limited value of syndromic management has been reasonably well-documented, there are limited data for the Asian-Pacific region. Moreover, the comparison of performance in three different groups adds strength to the manuscript. I have some comments that may help improve the manuscript.

Comment: The availability of data from three different populations is strength of the paper. However, Table 1 illustrates that these populations are very different with regards to bio-behavioural data (e.g. age, sex for money, etc.). Therefore, I think it is not appropriate to aggregate data anywhere in the manuscript (e.g. overall STI prevalence, overall prevalence of symptoms). Data should be presented stratified by study settings as is also done in table 4.

Response: The authors agree that the inclusion of data from three different clinical study populations is one of the strengths of this paper.

The manuscript has been revised to take the reviewer's comments into account (lines 15, 176-195 revised; 'Totals' column deleted and additional rows presenting clinical features added, Table 2; Table 3 deleted).

Comment: The methods section would benefit of additional information with regards to the three study settings: which 'type' of women usually access these services? Are these only for screening purpose or do only for symptomatic women? Also, 'well woman' clinic is not a widely known concept – what does this entail?

Response: Lines 87 – 93 have been revised to take these comments into account.

Comment: The results section would benefit from more detailed and structured information with regards to
a) prevalence of symptoms (and which ones), and
b) proportion of symptomatic/asymptomatic infections in each study population.
The conclusion (see strengths box at the first page) is that asymptomatic infections constitute a problem as these are not treated under the syndromic approach, but nowhere is clearly mentioned which proportion is asymptomatic.

Response: The current manuscript focuses on the performance of WHO-endorsed clinical algorithms for the detection and treatment of curable genital STIs among women in different clinical populations.

The results section of the manuscript provides data on the degree of over- and under-treatment observed in each clinical population (e.g. lines 201-228; 212-219; Table 3).

Comment: We know that performance of this algorithm for STIs is not going to be perfect due to a) asymptomatic infections, b) other (non)STIs causing similar symptoms. The use of these syndromic guidelines is not to 'detect' or 'diagnose' STIs, but to provide a basis for empirical treatment that may be correct or incorrect. Therefore, I think an outcome with regards to 'proportion correctly treated' and 'proportion overtreatment' (antibiotics given based on algorithm but none of the STIs present) and 'proportion undertreatment' (STI+ but not treated or treated with incorrect antibiotics based on the algorithm) may be more appropriate that the sens/spec/ppv/npv.

Response: The authors believe that it is more informative to present standard performance measures in this case in order to highlight the limitations of the syndromic management approach for STI detection and treatment compared with a laboratory-based reference (or 'gold') standard.

Comment: In addition to previous comment: it would be more appropriate to calculate the sens/spec/ppv/npv of the algorithm in symptomatic women only. Asymptomatic women would inherently be missed, setting the algorithm up for failure, but the question is still: how does the algorithm perform in symptomatic women? (Figure of speech: if this were to be good, the syndromic guidelines would still be useful).

Response: It is problematic to estimate performance measures among symptomatic women only. The purpose of the current study was to evaluate how well syndromic management is able to detect and treat underlying STIs. We were interested in performance among all women (symptomatic and asymptomatic) attending different clinical services in this setting because we wanted to better understand the degree of over- and under-treatment in this setting. An a priori assumption was that performance among women attending sexual health clinics (who have the highest prevalence of clinical symptoms and syndromic diagnoses; Table 3, pp14) would be superior to that observed in other clinical settings, but this was not observed in practice.

Comment: The results section could be condensed, especially description of the results in table 4; the highlights of this table could be presented in a few sentences instead of full page. This would allow to add some information (see previous paragraph).

Response: The results section has been extensively revised following comments above.

Comment: Would it be valuable for the authors to design a risk score based on the bio-behavioural and clinical data, using multiple regression analysis, to see if they could generate a (syndromic) algorithm with better performance in their context?

Response: We believe that this would be beyond the scope of the current manuscript, which focuses on the performance of WHO-endorsed clinical algorithms for the detection and treatment of curable genital STIs among women in different clinical populations.

Comment: The authors should decide about what they do with their HIV and syphilis data. Venepuncture is mentioned in the abstract, and HIV and lues testing in the results section, but they do not seem to present these data. Perhaps include these in table 1 with demographics?

Response: The authors do not believe that the inclusion of these data would add value to the current manuscript, given its focus and scope.

Comment: Would delete 'venepuncture' from the abstract.

Response: Removed – line 11

Comment: Abstract, objective: abbreviation PNG is not introduced earlier.

Response: Many thanks – now included in line 2.

Comment: Abstract: include reference to WHO guidelines as the reference standard.

Response: Journal-specific instructions for authors ask that references are not included within the Abstract.

Comment: References 1 and 2 appear missing from the introduction section, as the first reference mentioned is number 3.

Response: Reference numbering has been corrected in the current version of the manuscript.

Comment: How were the STIs diagnosed? Don't understand the mention of venepuncture in the methods section, which would suggest serology played a role?

Response: STIs were diagnosed using genital specimens (line 105-107).
Venepuncture specimens were collected for point-of-care HIV and syphilis tests only (line 107-108).

Comment: Introduction speaks of 'underdiagnosis' which should read 'undertreatment' as the syndromic algorithms do not provide a diagnosis but treat empirically.

Same for the last sentence of the introduction that provides the 'objective' of the paper: it's not about detecting STIs, but it's an indication for presumptive treatment that covers STIs.

Response: Changed from under-diagnosis to under-treatment (line 72); line 79 also revised as suggested.

Comment: Please elaborate on reference 12 and include a bit more information about the laboratory tests used to detect CT, NG and TV, include the name of the assay(s).

Response: Please elaborate on reference 12 and include a bit more information about the laboratory tests used to detect CT, NG and TV, include the name of the assay(s).
The correct reference is Ref#10, which provides detailed information on the real-time PCR assays used:

10. Vallely A, Ryan CE, Allen J, et al. High prevalence and incidence of HIV, sexually transmissible infections and penile foreskin cutting among sexual health clinic attendees in Papua New Guinea. Sex Health 2014;11(1):58-66. doi: 10.1071/sh13197 [published Online First: 2014/03/13]

Comment: Do the authors have any information about time since onset of symptoms? Does this impact on the performance of the algorithm?

Response: Data relating to onset of symptoms is not available. We assessed women based on their symptoms at time of consultation.

Comment: What drugs are used in Papua New Guinea to treat STIs?

And how are women with a previous/recent history of STI treatment evaluated in this algorithm? Did this affect performance of the algorithm?

Response: The authors believe that antibiotic regimens are not relevant to the current manuscript, but would be happy to provide if the Editorial team and/or reviewers feel this may be of additional interest. Previous or recent STI diagnosis/treatment was not included as part of algorithms evaluated in the current study.

Comment: The authors mention that BV and MG were not looked at in their study, but perhaps should also mention Candida infections.

Response: This section has been revised to take these comments into consideration (lines 258-260).

Reviewer: 2
Reviewer Name: Nigel Garrett
Institution and Country: Centre of the AIDS Programme of Research in South Africa (CAPRISA), South Africa
Please state any competing interests: None declared

The manuscript by Lisa Vallely and colleagues is a well written paper, which further highlights the inadequacies of the syndromic STI management care model in high burden and resource-constrained settings. This large cross-sectional evaluation was conducted among women presenting to three distinct clinical services in one of the highest STI burden countries (Papua New Guinea) globally. It confirms the high burden of STIs, and the low accuracy of predicting disease with the syndromic approach, and makes the case for a radical change to a point-of-care diagnostic care model. Although other groups have previously described the problems with syndromic management, this paper adds to the literature at an important time, when a switch to diagnostic testing is considered by the WHO.

Comment: 1. Page 4, line 38: Considering that most STI experts and the WHO agree that syndromic STI management is not ideal, it would be important to highlight some of the recent constructive discussions on how to transition from syndromic to diagnostic care. It may be worthwhile highlighting a recent WHO report ('Global health sector strategy on sexually transmitted infections 2016–2021. Towards ending STIs to the reader'). http://apps.who.int/iris/bitstream/10665/246296/1/WHO-RHR-16.09-eng.pdf?ua=1

Response: Many thanks for this suggestion. The final paragraph of the Discussion section (lines 296 – 306) has now been extensively revised and the WHO report cited.

Comment: 2. The authors should clarify what happened to women who were asymptomatic, i.e. received no syndromic treatment, but were diagnosed with one of the three STIs. Were these women contacted and offered treatment? If this group was not offered treatment, it is important for the reader to know that this was clearly addressed/ discussed during the consent process for the study.

Response: During the consent process, women in all clinic settings were advised to return for follow-up appointments in order to receive their STI test results. Locator information (including mobile telephone contact number) was collected from all participants to facilitate future follow-up e.g. to trace women in the community if they did not re-attend for scheduled clinical review.
Additional detail has been included in the revised manuscript (lines 104-105; lines 121-124).

Comment: 3. p.10, l.36: A high proportion of women reported abdominal pain (36.7%). This is higher than in previously reported studies, where vaginal discharge has been the most common symptom/sign. It would add to the manuscript, if the authors could expand on this phenomenon (in the results or discussion), in particular, whether they believe that the abdominal pain was due to PID (i.e. STI complication) or other causes, and whether these women received an extended course of antibiotics or not.

Response: Abdominal pain was a relatively common symptom in this setting and a syndromic diagnosis of lower abdominal pain syndrome (LAPS) was made in around one third of women attending well woman clinics and over 70% of women attending sexual health clinics (Table 3, revised manuscript). The syndrome is considered analogous to PID, and initial management comprises amoxicillin 500mg tds x5 days, plus metronidazole 400mg tds x5 days, plus doxycycline 100mg bd or azithromycin 500mg od x10 days.

Comment: 1. Page 7, line 13: Consider switching NPV and PPV to be consistent with the tables.

Response: Revised in the current manuscript as suggested (line 139-140, pp7).

Comment: 2. Table 1: Please double-check variables ‘vaginal sex in the last week’ and ‘no. of people had vaginal sex with in the last week’. It looks like the number of women who had sex in the last week differs (N=1062 vs N=1109). If this is correct, it may be worth explaining the difference in a footnote, e.g. the data was based on questionnaire or similar.

Response: These data are based on different sections of the study enrolment CRF and are correct.

Comment: 3. p.15, l.41: The authors say that BV (a vaginal syndrome) is ‘sexually transmitted’. While there is strong evidence that BV is ‘associated’ with sex, it is not usually described as ‘sexually transmitted’. Detailed microbiome studies are currently investigating, whether there are specific anaerobes, which contribute to BV, that are indeed ‘sexually transmitted’.

Response: Many thanks; this section has been revised (pp15, line 258)
Comment: 4. p15, l.49: Suggest to abbreviate BV higher up in the manuscript.

Response: Revised as suggested, many thanks.

Comment: 5. Given the high rates of asymptomatic STIs among antenatal attendees, it would be useful to add to the discussion the implications thereof, some of which are only mentioned in the Introduction (e.g. premature labour and low birth weight).

Response: Many thanks; this section has now been revised (pp15, line 242-244).

Reviewer: 3
Reviewer Name: Jillian Pintye
Institution and Country: Department of Global Health, University of Washington, Seattle, USA
Please state any competing interests: None declared

This is a well written paper about an important issue affecting women and infants worldwide. The authors present an evaluation of syndromic management of curable STIs among women attending ANC and SRH clinics in Papua New Guinea, a setting with significant STI burden. The methods are sound and the interpretation of results is appropriate. I have a few specific comments to strengthen this manuscript:

Comment: Introduction
1. The authors state that PNG "...has among the highest estimated prevalences of genital chlamydia, gonorrhoea and trichomonas of any country in the Asia-Pacific region",. However, the actual % compared to that of other countries would be a stronger set up. Consider re-phrasing to, "The prevalence rates of CT, GC and TV within the Asia-Pacific region are XX%, XX% and XX%, respectively. Among all countries within the region, PNG is among the highest prevalence countries for all three infections with rates of XX% for CT, XX% for GC and XX% for TV" or something to that effect that compares the PNG rates with the overall regional rates.

Response:
Many thanks for these comments. In order to ensure the manuscript remains as concise as possible we elected not to provide such detail but to provide an overview only (with relevant references cited). We believe that the data we present in the manuscript further exemplified our statement in regards the high prevalences of STIs in this setting.

Comment: Study design and procedures
2. It's important that to distinguish that you are evaluating "diagnostic" performance of syndromic algorithms rather than other types of performance (ie economic, etc). I suggest include "diagnostic" when indicating that you are evaluating "performance".

Response: Line 91-93 have been revised as follows:
“A key objective of the study was to evaluate the clinical performance of syndromic STI diagnosis for the treatment of curable genital STIs among different clinical populations in this setting.”

Comment: 3. How and when were PCR results returned to clients? Were antimicrobials administered to participants free of charge? Were all clients treated?
It is important to include these details or at least note that participants with lab-confirmed infections were treated per PNG Ministry of Health guidelines and then cite the guidelines.

Response: Please see pp6-7 of the revised manuscript (lines 112-123). PNG guidelines are cited (Ref#9).

Comment: Results
4. Appropriately, the results are presented stratified by clinic entry point. It would be helpful to reference the rationale for this approach in the methods and perhaps even in the intro (ie prevalence rates vary by female subpopulations and may present differently and/or have different epidemiological trends). As is, it's not clear why the authors decided to present the results stratified as this approach is only introduced in the results.

Response:
Please see pp6 of the revised manuscript, lines 86-95.

Comment: Discussion
5. The first paragraph is mainly restating the findings. It is very helpful to include the impact statements (ie XX% of infections would have been missed without lab testing), but it would also be helpful to tie these findings to a larger public health message. For example, why does it matter that so many infections would be missed? How might this contribute to the overall burden of adverse perinatal/MCH outcomes in this setting? Are these findings different than other similar studies or rather to they contribute to the growing evidence that additional POC diagnostics are needed for STIs, specifically within the context of ANC, etc? These details would strengthen the discussion's first paragraph rather than simply restating the results.

Response:
We believe that a detailed discussion of these important points may be beyond the scope of the current manuscript but do make reference to these issues in the Discussion section of the revised manuscript (lines 242-244; 297-306)

Comment: 6. The organization of the discussion could be strengthened. It seems odd to call out the lack of M. gen and BV testing but not discuss the other very interesting findings. For example, the prevalence of CT is quite high (>20%) among ANC clients and then low (~7%) among well women. Was this finding expected? How does this compare to similar settings? A discussion about these results are warranted rather then the BV and M. gen details as the evidence base for those STIs causing adverse perinatal outcomes is less strong than CT, GC, and TV.

Response: The focus of the Discussion section (and the manuscript overall) is the performance of syndromic management. We have previously described the high burden of STIs among women and men in different clinical and community settings in PNG (e.g. Refs#6-8, 10 in the current manuscript); and are currently conducting a cluster randomised trial to evaluate antenatal point-of-care STI testing and treatment to improve birth outcomes in low-income settings (http://www.isrctn.com/ISRCTN37134032)

Comment: 7. Condense the limitations to one paragraph and raise these concerns later in the discussion, after grounding your findings to the existing literature and explaining the implications of your results (ie need for further POC testing in LMICs, substantial burden of STIs associated with adverse perinatal outcomes among pregnant women, etc).

Response: We have made a number of changes to the Discussion section in the revised version of the manuscript and would like to retain the current structure and sequence.

VERSION 2 – REVIEW

REVIEWER	Remco Peters Anova Health Institute, South Africa
REVIEW RETURNED	19-Sep-2017

GENERAL COMMENTS	No further comments.

REVIEWER	Nigel Garrett CAPRISA, South Africa
REVIEW RETURNED	15-Sep-2017

GENERAL COMMENTS	The authors have adequately addressed all my previous comments.

REVIEWER	Jillian Pintye University of Washington, Department of Global Health, USA
REVIEW RETURNED	24-Sep-2017

GENERAL COMMENTS	This is a revision of an interesting manuscript that this reviewer previously reviewed. The authors have adequately addressed all major concerns raised during the last peer review as described in the thorough response letter. The manuscript is greatly improved. My one (very minor) comment is that the term "prevlances" is used in multiple places. In epidemiological manuscripts, it is conventional to simply use "prevalence" or "prevalence rates" when describing results for multiple pathogens. This may be a regional language variation and I defer for the editorial team for guidance. Otherwise, the revised version is nice contribution to the literature and will support the WHO's move towards diagnostic approaches for STI management.

VERSION 2 – AUTHOR RESPONSE

Reviewer 3:
I have considered the request of reviewer 3 and altered the manuscript, changing prevalences to prevalence in some sections of the manuscript.